REMARKS

By the present amendment claims 80, 106, and 107 have been canceled without prejudice. Applicants reserve the right to prosecute the subject matter of canceled claims 80, 106, and 107 in one or more related applications.

Applicants have also amended claims 69, 71-74, 79, 81-85, 93, 94, and 99-105 for purposes of clarity by the present amendment. In particular, the amended claims now recite drug in place of substance. Support for the recitation of drug can be found at, for example, paragraph 26, line 1 and paragraph 49, lines 1-3.

Claims 69 and 85 have also been amended to recite that the systemic bioavailability of the drug is measured by a determination of its AUC. Support for the bioavailability being measured by a determination of the area under the curve (AUC) can be found at, for example, paragraph 12, lines 1-3. No new matter has been added.

After entry of the above-made amendments, claims 69-75, 77-79, 81-95, and 97-105 will be pending,.

I. REQUEST FOR CLARIFICATION OF THE STATUS OF THE PENDING REJECTIONS

In the Office Action the Examiner stated that that Applicants' arguments filed June 7, 2007 were persuasive and that the previous rejections of the claims have been withdrawn (see Office Action at page 2, first paragraph). However, while noting that the rejection of claims 59-75, 77-89, 93-95 and 97-104 as being unpatentable over U.S. Patent No. 5,527,288 to Gross *et al.* in view of U.S. Patent No. 6,007,821 to Srivastava *et al.* (Srivastava) is now absent, the Office Action repeats the rejection of claims 69-75, 77-89, 90-95 and 97-104 as allegedly being unpatentable over U.S. Patent No. 5,250,023 to Lee *et al.* (Lee) in view of Srivastava at pages 5-6 of the Office Action. Applicants respectfully request clarification as to whether the Examiner has, in fact, maintained the rejection of the claims as allegedly being unpatentable over Lee in view of Srivastava. Notwithstanding, in order to be fully responsive to the Office Action, Applicants have set forth remarks in Section III below addressing the rejection of the claims over Lee in view of Srivastava.

II. THE CLAIMS ARE PATENTABLE OVER U.S. PATENT NO. 5,527,288 TO GROSS *et al.* IN VIEW OF U.S. PATENT NO. 6,007,821 TO SRIVASTAVA *et al.*

Claims 69-75, 77-89, 93-95 and 97-104 are rejected over U.S. Patent No. 5,527,288 to Gross *et al.* (Gross) in view of U.S. Patent No. 6,611,707 to Prausnitz *et al.* (Prausnitz) in further view of U.S. Patent No. 6,007,821 to Srivastava *et al.* (Srivastava). Specifically, the Examiner contends that Gross teaches an intradermal compartment drug delivery device. The Examiner concedes that Gross fails to disclose that its device has a needle with an exposed height between 0 and 1 mm, but contends that Prausnitz teaches needles with a zero exposed height to deliver drugs into the skin. The Examiner asserts that it would have been obvious to use the teaching of the exposed needle outlet of Prausnitz in the invention of Gross to provide a longitudinally directed flow of liquid from the needle opening.

The Examiner also concedes that Gross fails to disclose that a substance can be administered at a reduced dose (10-30%) to achieve the same level of systemic bioavailability as compared to subcutaneous administration. However, the Examiner relies on Srivastava for the teaching that intradermal injections require a lower dosage than subcutaneous injections in a method for treating autoimmune diseases. The Examiner contends that it would have been obvious to use the invention of Gross to administer the composition at a reduced intradermal dosage as taught by Srivastava. For the following reasons, Applicants respectfully disagree.

A. The Legal Standard

In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 U.S.P.Q.2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 U.S.P.Q. at 467; *see also* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* ("Examination Guidelines"), Federal Register, Vol. 72, No. 195, October 10, 2007, pages 57527-57528. The Supreme Court stated that in determining obviousness, "a court must ask whether the improvement is more than a predictable use of prior art elements according to their

established functions." *KSR*, 127 S.Ct. at 1740, USPQ2d at 1396. The Supreme Court also stated that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does...." *KSR*, 127 S.Ct. at 1741, 82 U.S.P.Q.2d at 1396.

B. Claims 69-75, 77-79 and 81-84

Claim 69 has been to amended recite a method for delivering a drug into an intradermal compartment of a human subject's skin comprising administering the drug through at least one small gauge hollow needle having an outlet with an exposed height between 0 and 1 mm; said outlet being inserted into the skin to a depth of between 0.3 and 2 mm, such that delivery occurs between 0.3 and 2 mm. Claim 69, as amended, further specifies that the dosage of the drug administered into the intradermal compartment for achieving a systemic bioavailability of the drug is reduced by at least 10% compared to the dose required to achieve the systemic bioavailability when the drug is delivered to a subcutaneous compartment of the human subject's skin, wherein the systemic bioavailability of the drug is measured by a determination of its AUC.[1] Claims 70-75, 77-79, and 81-84 all depend directly or indirectly on claim 69, and therefore incorporate by reference each and every recited feature of claim 69.

The Examiner relies on the combination of Gross and Prausnitz to provide the suggestion of the needle outlet height of 0 to 1 mm (hereinafter, "the claimed needle configuration") and needle outlet insertion depth as recited in claim 69; and is relying on Srivastava to provide the suggestion of the dose sparing effect for the drug. However, as elaborated further in the remarks below, the combination of Gross and Prausnitz fails to teach or suggest the claimed needle configuration and outlet insertion depth, and Srivastava fails to teach or suggest that intradermal delivery results in the claimed dose sparing effect for the drug.

1. The Combination of Gross and Prausnitz Fails To Teach or Suggest the Claimed Needle Configuration and Insertion Depth

Gross describes an infusion device to deliver a drug below the epidermis; *i.e.*, to the interface between the epidermis and dermis, or to the interior of the dermis, or

[1] For ease of reference, this feature of the claimed methods will be referred to hereinafter as "the dose sparing effect for the drug".

subcutaneously (Gross col. 3, *ll.* 46-50). To this end, Gross describes a needle that projects outward from the housing preferably by approximately 0.3 to 3 mm, and most preferably 0.3 to 1 mm (Gross col. 2, *ll.* 16-20, and col. 4, *ll.* 18-22).

Gross is silent as to the configuration of the needle outlet, and does not correlate the depth of the outlet to any one of the delivery sites. Gross does not teach the depth or thickness of the layers of skin or boundaries of the intradermal compartment. Gross does not teach that the depth and exposed height of the outlet must be contained within the intradermal compartment to achieve the presently claimed dose sparing effect for the drug. In the absence of this recognition, Gross proposes a range of needle lengths for his device that would not necessarily confine the needle outlet to the targeted intradermal compartment as required by the claims, and therefore, would fail to achieve the dose sparing effect for the drug.

Applicants respectfully submit that the Examiner' reliance on Prausnitz for the use of microneedles having blunt or flat tips; *i.e.*, an exposed outlet height of 0 is misplaced because Prausnitz teaches away from delivery to the dermis and should not be combined with Gross. In particular, Prausnitz describes transdermal devices that are designed to penetrate the epidermis – not the dermis – in order to avoid contacting nerves which may cause pain. While microneedles that may have blunt or flat tips are described, Prausnitz recommends that these needles penetrate at a depth of less than 100-150 μm, so as to only deliver to the epidermis and *avoid penetrating into the dermis* (*see*, Prausnitz at col. 4, *ll.* 7-11) (emphasis added). See the passage below as excerpted from Prausnitz:

> In transdermal applications, the "insertion depth" of the microneedles is preferably less than about 100-150 μm, so that insertion of the microneedles into the skin does not penetrate into the dermis, thereby avoiding contacting nerves which may cause pain. In such applications, the actual length of the microneedles typically is longer, since the portion of the microneedles distal the tip may not be inserted into the skin, the uninserted length depends on the particular device design and configuration. The actual (overall) height or length of microneedles should be equal to the insertion depth plus the uninserted length."

(Prausnitz at col. 4, *ll.* 7-11). Thus, the Examiner's proposed use of a flat-tipped needle in Gross's device with a needle projection of 0.3-3.0 mm (Gross col. 4, *ll.* 18-19) would contravene Prausnitz's own teaching that the flat-tipped needle not be applied deeper than 0.15 mm (or 150 μm) to avoid penetrating into the dermis and contacting nerves. Since Prausnitz teaches away from delivery to the intradermal compartment it cannot be used to

supply the claimed needle configuration and insertion depth missing from Gross. Applicants further note that Srivastava does not remedy this deficiency because it fails to disclose any needle configurations.

By failing to consider the cited references in their entireties, including portions that would lead away from the claimed invention, the Examiner has erroneously found motivation to combine the cited references, where, in fact, none exists. See *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); M.P.E.P. at p. 2100-126.

2. Srivastava Fails To Teach or Suggest the Claimed Dose Sparing Effect for the Drug

As noted above, the claims have been amended to recite drug in place of substance. As the Examiner admits, Gross is silent with respect to the claimed dose sparing effect for the drug. To fill this gap, the Examiner relies on Srivastava, col. 19, *l.* 60 – col. 20, l. 10) – but this analysis is flawed because Srivastava describes methods of administering vaccines and not administration of *drugs* as recited in the amended claims. Vaccines are not distributed systemically in the bloodstream, and as a result do not display pharmacokinetic profiles from which an area under the curve (AUC) for the injected antigen could be determined. Here, Srivastava describes using heat shock protein ("hsp") as an adjuvant that modulates the immune response at col. 19, *l.* 60 to col. 20, *l.* 25. Tellingly, Srivastava specifically acknowledges that the hsp effect "is mediated through the endogenous, *local, cellular response instead of systemically.*" (Srivastava, col. 6, *ll.* 9-13, emphasis supplied).

Pharmacokinetic studies are meaningless in the vaccine art because practitioners in this field do not gauge the potency of a vaccine by its ability to be circulated in the bloodstream – that is why Srivastava does not report a pharmacokinetic profile. Rather, a vaccine's efficacy is measured by assessing the body's immunological response to the antigen; *e.g.*, the cellular and antibody responses generated against the vaccine antigen that is introduced locally – these are the gauges described in the portion of Srivastava cited by the Examiner – not pharmacokinetic profiles of antigen.

In sum, none of the references taken alone or in combination describe or suggest administration via a needle having the claimed configuration and placement in the intradermal compartment. The references taken alone or in combination are equally silent as to the dose sparing effect for the drug achieved when is delivered intradermally.

Accordingly, Applicants request that the rejection of claims 69-75, 77-79 and 81-84 under 35 U.S.C. § 103(a) be withdrawn.

B. Claims 85-95 and 97-105

Claim 85 had been amended to recite a method of delivering a drug into an intradermal compartment of a human subject's skin, said method comprising injecting or infusing the drug intradermally through one or more microneedles having a length sufficient to penetrate the intradermal compartment and an outlet at a depth within the intradermal compartment. Claim 85, as amended, further specifies that the dosage of the drug administered into the intradermal compartment is reduced by at least 10% compared to the dose required to achieve the systemic bioavailability when the drug is delivered to a subcutaneous compartment of the human subject's skin, wherein the systemic bioavailability of the drug is measured by a determination of its AUC. Claims 86-95 and 97-105 all depend directly or indirectly on claim 85, and therefore incorporate by reference each and every recited feature of claim 85.

The Examiner relies on the combination of Gross and Prausnitz to provide the suggestion of the microneedle outlet insertion depth as recited in claim 85; and is relying on Srivastava to provide the suggestion of the dose sparing effect for the drug. However, as elaborated further in the remarks below, the combination of Gross and Prausnitz fails to teach or suggest the microneedle outlet insertion depth as recited in claim 85, and Srivastava fails to teach or suggest that intradermal delivery results in the claimed dose sparing effect for the drug.

1. The Combination of Gross and Prausnitz Fails To Teach or Suggest the Claimed Microneedle Outlet Depth with the Intradermal Compartment

As noted above, Gross describes an infusion device to deliver a drug below the epidermis; *i.e.*, to the interface between the epidermis and dermis, or to the interior of the dermis, or subcutaneously (Gross col. 3, *ll.* 46-50). To this end, Gross describes a needle that projects outward from the housing preferably by approximately 0.3 to 3 mm, and most preferably 0.3 to 1 mm (Gross col. 2, *ll.* 16-20, and col. 4, *ll.* 18-22).

Gross does not correlate the depth of the outlet to any one of the delivery sites. Gross does not teach the depth or thickness of the layers of skin or boundaries of the intradermal compartment. Gross does not teach that the depth and exposed height of the needle outlet must be contained within the intradermal compartment to achieve the presently claimed dose

sparing effect for the drug. In the absence of this recognition, Gross proposes a range of needle lengths for his device that would not necessarily confine the needle outlet to the targeted intradermal compartment as required by the claims, and therefore, would fail to achieve the dose sparing effect for the drug.

Prausnitz, as noted above, teaches away from delivery to the dermis and should not be combined with Gross. Prausnitz describes transdermal devices that are designed to penetrate the epidermis – not the dermis – in order to avoid contacting nerves which may cause pain. In other words, Prausnitz teaches avoiding penetration into the dermis (*see*, Prausnitz at col. 4, *ll.* 7-11). Thus, the Examiner's proposed use of the needle as disclosed in Prausnitz in Gross's device with a needle projection of 0.3-3.0 mm (Gross col. 4, *ll.* 18-19) would contravene Prausnitz's own teaching that its needle not be applied deeper than 0.15 mm (or 150 μm) to avoid penetrating into the dermis and contacting nerves. Since Prausnitz teaches away from delivery to the intradermal compartment it cannot be used to supply the claimed microneedle outlet insertion depth missing from Gross. Applicants further note that Srivastava does not remedy this deficiency because it fails to disclose any needle outlet insertion depths.

2. Srivastava Fails To Teach or Suggest the Claimed Dose Sparing Effect for the Drug

As noted above, the claims have been amended to recite drug in place of substance. As the Examiner admits, Gross is silent with respect to the claimed dose-sparing effect for the drug that results from practice of the claimed method. To fill this gap, the Examiner relies on Srivastava (col. 19, *l.* 60 – col. 20, l. 10) – but this analysis is flawed because Srivastava describes methods of administering vaccines and not administration of *drugs* as recited in the amended claims. Vaccines are not distributed systemically in the bloodstream, and as a result do not display pharmacokinetic profiles from which an AUC for the injected antigen could be determined. Here, Srivastava describes using heat shock protein ("hsp") as an adjuvant that modulates the immune response at col. 19, *l.* 60 to col. 20, *l.* 25. Tellingly, Srivastava specifically acknowledges that the hsp effect "is mediated through the endogenous, *local, cellular response instead of systemically.*" (Srivastava, col. 6, *ll.* 9-13, emphasis supplied).

Pharmacokinetic studies are meaningless in the vaccine art because practitioners in this field do not gauge the potency of a vaccine by its ability to be circulated in the bloodstream – that is why Srivastava does not report a pharmacokinetic profile. Rather, a

vaccine's efficacy is measured by assessing the body's immunological response to the antigen; *e.g.*, the cellular and antibody responses generated against the vaccine antigen that is introduced locally – these are the gauges described in the portion of Srivastava cited by the Examiner – not pharmacokinetic profiles of antigen.

In sum, none of the references taken alone or in combination describe or suggest administration via a needle wherein the microneedle outlet is placed within the intradermal compartment. The references taken alone or in combination are equally silent as to the dose sparing effect for the drug achieved when it is delivered intradermally. Accordingly, Applicants request that the rejection of claims 85-95 and 97-105 under 35 U.S.C. § 103(a) be withdrawn.

Additionally, it should be noted that in response to the Examiner's contention that Applicants provide no quantitative or relative measure for the term "bioavailability" (*see* page 7, paragraph 2 of the Office Action), claims 69 and 85 have been amended to recite that the systemic bioavailability of the drug is measured by a determination of its AUC.

III. THE CLAIMS ARE PATENTABLE OVER U.S. PATENT NO. 5,250,023 TO LEE *et al.* IN VIEW OF U.S. PATENT NO. 6,007,821 TO SRIVASTAVA *et al.*

Claims 69-75, 77-89, 90-95 and 97-107 are rejected over U.S. Patent No. 5,250,023 to Lee *et al.* (Lee) in view of U.S. Patent No. 6,007,821 to Srivastava *et al.* (Srivastava). Specifically, the Examiner contends that Lee teaches an intradermal compartment drug delivery device that administers a substance through a hollow needle array and notes the devices shown in Figures 1 and 2 of Lee. The Examiner concedes that Lee fails to disclose that the dosage for the substance for achieving systemic bioavailability is reduced by 10-30% when administered to the intradermal compartment as compared to when the substance is delivered to the subcutaneous compartment. The Examiner relies on Srivastava for the teaching that intradermal injections require a lower dosage than subcutaneous injections in a method for treating autoimmune diseases. The Examiner alleges that it would have been obvious to use the invention of Lee to administer the composition at a reduced intradermal dosage value as taught by Srivastava. For the following reasons, Applicants respectfully disagree.

The rejection is improper because Lee, in fact, does not disclose a method or device for delivering a drug into an intradermal compartment of a human subject's skin, wherein a drug is administered *through* a hollow needle or microneedle as specified by the claims. The

disclosure of Lee as a whole makes apparent that the methods disclosed therein fail to rely on delivering a drug *through* a hollow needle or microneedle as the claimed methods require. Instead, Lee discloses that the needles form pathways through the skin. See, *e.g.*, the Abstract; col. 5, *ll.* 36-39; col. 5, *ll.* 44-50; and col. 6, *ll.* 32-38.

Both devices disclosed in Lee, an integration-type device and a separation-type device, clearly do not rely on delivery of a drug *through* a hollow needle or microneedle for administration into the skin. For instance, in describing the administration of a hydrophilic drug using the integration-type device (shown in Figure 1), Lee discloses that "the pa[th]way formed by skin needle[](**4**) is temporarily closed by the swelling of skin" in the absence of applying an electrical current to the pathway formed by a skin needle. *See* col. 5, *ll.* 44-50. Application of electrical current is said to cause contraction of the skin and open the pathway of the epidermis layer. *See* Lee at col. 5, *ll.* 51-57. This phenomena described in Lee is clearly inconsistent with a method in which a drug is actually delivered through a hollow needle or microneedle as the claimed methods require, where any skin swelling would fail to prevent delivery of the drug through a lumen of a steel needle.

Similarly, Lee's method for administering a drug from a separation-type device (shown in Figure 2) clearly does not rely on delivery through hollow needles or microneedles. In connection with using the separation-type device, Lee discloses "[l]ightly compressing a skin needle plate[](**15**) on the skin, and forming the drug delivery pathway on skin, and removing the skin needle plate(**15**), and on that skin, compressing the patch body[](**30**) ...." Col. 6, *ll.* 33-37. In other words, the needles are not in the skin at the time when the drug is actually delivered.[2] Thus, the separation-type device in Lee does not rely on delivering drug through hollow needles or microneedles.

Accordingly, Lee does not give reason to one of ordinary skill in the art to deliver a drug through a hollow needle or microneedle, let alone teach or suggest delivering a drug with the configurations recited by claims 69 and 85 and their dependent claims. Moreover since Srivastava does not disclose a depth in which a needle outlet is positioned within the skin, a feature which characterizes the methods recited in the present claims, it is clear that the claimed methods are not a combination of known elements. *Cf. KSR.*

Accordingly, for the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the rejection.

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[2] Moreover, Applicants note that Lee teaches that the use of needles can be avoided altogether by using an electric razor to alleviate the resistance of the epidermis layer. Col. 6, *ll.* 40-45.

CONCLUSION

Entry of the foregoing amendments and remarks into the record of the above-identified application is respectfully requested. Applicants submit that the amendments and remarks made herein now place the application in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

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Respectfully submitted,

Date: February 26, 2009

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